


# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 16466-WO-03	<b>FOR FURTHER ACTION</b>		See Form PCT/PEA/416
International application No. PCT/AL2005/000053	International filing date (day/month/year) 14.01.2005	Priority date (day/month/year) 15.01.2004	
International Patent Classification (IPC) or national classification and IPC INV. A61K31/352 A61K31/122 C07C50/30 C07D311/80 A61P35/00 A61P17/06 A61P33/02 A61P33/00 A61P29/00 A61P37/00			
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY...et al			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 16 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input checked="" type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand  10.11.2005		Date of completion of this report  20.04.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized officer  A. Jakobs  Telephone No. +31 70 340-2617	



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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-42 as originally filed

**Claims, Numbers**

1-43 as amended (together with any statement) under Art. 19 PCT

**Drawings, Sheets**

1-13 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☒ the claims, Nos. 19,22,24
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-13,24,34-42 (partially

because:

☒ the said international application, or the said claims Nos. 1-12 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1,11,13,24,34-42 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-18,20-22,27,31-33,43
	No: Claims	19,23-26,28-30,34-42
Inventive step (IS)	Yes: Claims	1-18,20-22,27,31-33,43
	No: Claims	19,23-26,28-30,34-42
Industrial applicability (IA)	Yes: Claims	see separate sheet
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Re Item III.**

Claims 1-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Present claims relate to an extremely large number of possible compounds/products/apparatus/methods.

Originally filed claims 1,7,13,23,35,37,38,41 (amended claims 1,11,13,24,34-42) relate to a compound, use or method defined by reference to the following parameters: inhibition of hyperproliferation, cannabinoic quinone; or relate to an unsupported number of compounds (e.g. wherein A is a 5, or 7-membered ring).

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Furthermore, support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the claims 2-6,8-12,14-22,24-34,36,39,40,42-50, and 1,7,13,23,35,37,38,41 (partially and as far as encompassed within the completely searched claims) as originally filed, i.e. amended claims 2-10,12,14-23,25-33 and 1,11,13,24,34-42 (partially).

No Preliminary Examination will be performed with respect to subject matter which is not covered by the search report.

**Re Item V.**

- 1 Reference is made to the following documents:  
D1 : USAMI, NORIYUKI ET AL: ".DELTA.8-Tetrahydrocannabinol p-quinone as an

- air oxidation product of .DELTA.8-tetrahydrocannabinol and its biological and pharmacological effects in mice" RESEARCH COMMUNICATIONS IN ALCOHOL AND SUBSTANCES OF ABUSE , 18(3 & 4), 125-139 CODEN: RCAAEE3; ISSN: 1080-8388, 1997, XP008048264
- D2 : USAMI, NORIYUKI ET AL: "Inhibition of mouse hepatic glutathione S-transferase by .DELTA.8-tetrahydrocannabinol p-quinone and cannabidiol hydroxyquinone" RESEARCH COMMUNICATIONS IN ALCOHOL AND SUBSTANCES OF ABUSE , 20(1 & 2), 53-68 CODEN: RCAAEE3; ISSN: 1080-8388, 1999, XP008048265
- D3 : EDERY, HABIB ET AL: "Structural requirements for cannabinoid activity" ANNALS OF THE NEW YORK ACADEMY OF SCIENCES , 191, 40-53 CODEN: ANYAA9; ISSN: 0077-8923, 1971, XP08048273
- D4 : EDERY, H. ET AL: "Structure-activity relations in the tetrahydrocannabinol series. Modifications on the aromatic ring and in the side-chain" ARZNEIMITTEL-FORSCHUNG , 22(11), 1995-2003 CODEN: ARZNAD; ISSN: 0004-4172, 1972, XP008048340
- D5 : WATANABE, KAZUHITO ET AL: "Inhibitory effect of cannabidiol hydroxyquinone, an oxidative product of cannabidiol, on the hepatic microsomal drug-metabolizing enzymes of mice" JOURNAL OF PHARMACOBIO-DYNAMICS , 14(7), 421-7 CODEN: JOPHDQ; ISSN: 0386-846X, 1991, XP008048261
- D6 : HONORIO, K. M. ET AL: "A quantum chemical study on the psychoactivity of cannabinoid compounds" THEOCHEM , 538, 99-106 CODEN: THEODJ; ISSN: 0166-1280, 2001, XP008048255
- D7 : BORNHEIM, LESTER M. ET AL: "Characterization of Cytochrome P450 3A Inactivation by Cannabidiol: Possible Involvement of Cannabidiol-Hydroxyquinone as a P450 Inactivator" CHEMICAL RESEARCH IN TOXICOLOGY , 11(10), 1209-1216 CODEN: CRTOEC; ISSN: 0893-228X, 1998, XP008048254
- D8 : KOGAN, NATALYA M. ET AL: "Synthesis and Antitumor Activity of Quinonoid Derivatives of Cannabinoids" JOURNAL OF MEDICINAL CHEMISTRY , 47(15), 3800-3806 CODEN: JMCMAR; ISSN: 0022-2623, 2004, XP008048256

2. Allowability of amended claims 19,22,24:

- 2.1 The amendments introduced in said claims (former claims 46,48,1 respectively) are not allowable because they were not disclosed in the application as filed. A disclaimer which is or becomes relevant for the assessment of inventive step or sufficiency of disclosure adds subject-matter contrary to Article 19 (2) PCT.

**3 CLAIMS 19,23-26,28-30,34-42**

- 3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 24,25,29,30,34-42 is not new in the sense of Article 33(2) PCT.

Document D1 discloses (see the passages cited in the search report) tetrahydrocannabinol p-quinone (HU-336), pharmaceutical compositions comprising said compound and its biological and pharmacological (analgesic, antiemetic, pentobarbital-induced sleep prolongation, ...) effects in mice. In particular, the pharmaceutical compositions per se of claims 34-42 are not rendered novel by their intended use.

- 3.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 24-26,28,29,30,34-42 is not new in the sense of Article 33(2) PCT.

Document D2 discloses (see the passages cited in the search report) the compounds HU-331 (cannabidiol hydroxy-quinone) and HU-336 (delta 8 tetrahydrocannabinol p-quinone, delta 8-THCPQ), pharmaceutical compositions comprising these compounds and their inhibitory effect on mouse hepatic glutathione S-transferase, and discloses that these compounds may have some pharmacological effects similar to other quinone compounds like menadione or adriamycin.

- 3.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 24,25,29,30,34-42 is not new in the sense of Article 33(2) PCT.

Document D3 discloses (see the passages cited in the search report) the cannabinoid activity of HU-336, denominated delta 6 THC quinone.

- 3.4 The present application does not meet the criteria of Article 33(1) PCT, because the

subject-matter of claim 24,25,29,30,34-42 is not new in the sense of Article 33(2) PCT.

Document D4 discloses (see the passages cited in the search report) the cannabinoid activity of delta 8 THC quinone, i.e. HU-336 (which is called delta 6 THC quinone in the publication).

- 3.5 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 19,23-26,28,30,34-42 is not new in the sense of Article 33(2) PCT.

Document D5 discloses (see the passages cited in the search report) the inhibitory effect of cannabidiol hydroxyquinone, an oxidative product of cannabidiol, on the hepatic microsomal drug-metabolizing enzymes of mice, which is a pharmacological effect anticipating the pharmaceutical compositions comprising said compound HU-331.

- 3.6 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 24,25,29,30,34-42 is not new in the sense of Article 33(2) PCT.

Document D6 discloses (see the passages cited in the search report) a quantum chemical study on the psychoactivity of cannabinoid compounds, including delta 8 THC quinone which anticipates the pharmaceutical compositions comprising the compound HU-336.

- 3.7 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 19,23-26,28,30,34-42 is not new in the sense of Article 33(2) PCT.

Document D7 discloses (see the passages cited in the search report) the compound cannabidiolhydroxyquinone (HU-331), and its possible involvement as a P450 cytochrome inhibitor. P450 is responsible for metabolizing more than 60% of clinically prescribed drugs, and therefore D7 also anticipated pharmaceutical compositions comprising HU-331.

**4 CLAIMS 19,23-26,28-30,34-42**

Claims 19,23-26,28-30,34-42 do not contain any features which, in combination with



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the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

**5 CLAIMS 1-18,20-22,27,31-33,43**

The combination of the features of claims 1-18,20-22,27,31-33,43 are neither known from, nor rendered obvious by, the available prior art. The reasons are as follows: the compounds of said claims are novel, and their use in therapy is also new and inventive.

